(ii) do not occur in the same protein in nature in the order in which they are present in the chimeric protein; or

(iii) do not occur in nature with the same spacing that is present in the chimeric protein.

47. (**Amended**) The nucleic acid of claim 46, wherein the zinc finger motif is from a protein selected from the group consisting of transcription factor IIIA, Zif268, SW15, Krüppel, Hunchback, and a steroid receptor.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made." For the convenience of the Examiner, all claims being examined, whether or not amended, are presented in that section.

REMARKS

Claims 40-70 and 72-98 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note that the CPA has been established, and claims 1-21, 24, 27-30, 34, and 36 are withdrawn.

I. The pending claims meet the written description requirement

Claims 40-70 and 72-98 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner does not assert that the terms recited in the pending claims lack support in the

specification. Rather, the Examiner appears to contend that without teaching all naturally occurring sequences – which would fall outside the scope of the pending claims – Applicants' disclosure fails to reasonably convey possession of the subject matter defined by the claims. Applicants respectfully traverse this rejection.

The point of the written description requirement is that it "guards against the inventor's [later] overreaching by insisting that he recount his invention in such detail that his future claims can be encompassed within his original creation." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555 (Fed. Cir. 1991). The fundamental factual inquiry is whether one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention at the time of filing. Applicants respectfully submit that the specification clearly conveys that the Applicants had possession of the subject method of the pending claims.

The Examiner further suggests that Applicants have failed "to disclose even one embodiment that definitively meets the claim limitations because the specification does not teach that any one embodiment is definitively not present in nature." Applicants assert that this line of arguing by the Examiner is not an appropriate ground for maintaining a rejection under 25 USC §112. However, assuming *arguendo* that the such a requirement were made of the Applicants, the correct standard for determining compliance with the Written Description requirement of section 112 is one of reasonableness. The fact remains that one of ordinary skill in the art would reasonably believe that the various working examples of the present application represent proteins which do not exist in nature, and the Examiner has not provided any factual basis, in the form of cited prior art or an Examiner's declaration, on which an argument to the contrary could be reasonably based.

In the field of synthetic chemistry, for example, when one invents novel compounds, an applicant is not required by the description or other requirements to prove definitively that any or all of the included species is not found in nature or to teach how to determine whether a given compound is found in nature. Claims to those new compounds are not rejected as products of nature because they might occur in nature or over the art because there might be novelty-barring prior art. The claims are properly rejected only if they are shown to encompass species which are known to occur in nature or which were disclosed in identifiable and cited prior art. Similarly, claims to assertedly

novel compounds are not rejected under the description requirement on the grounds that an applicant has not disclosed all known compounds or all compounds which might occur in nature, e.g., disclosed the full scope of the prior art.

In this case, applicants' specification clearly describes the claimed subject matter and enables its use—consistent with precedents like In re Wands. The claimed products comprise components which may themselves occur in nature, but which are recombined by human design and/or intervention. The "non-naturally occurring" and conceptually similar language used by applicants are long accepted claim language which do not raise description requirement (or enablement, see below) issues.

The final guidelines for section 112 clearly state there is a strong presumption that the specification as filed provides adequate written description support for the claimed invention. See *Guidelines*, 64 Fed. Reg. 71 at page 1105. A disclosure as filed is prima facie adequate. To support a rejection, the PTO has the burden of showing why the Applicant's evidence is insufficient. In any case where lack of written description is found, the PTO should cite documentary evidence in support of the finding. As expressly stated by the guidelines, where documentary evidence is not available, technical reasoning, as distinguished from legal reasoning, may support the finding when the technical line of reasoning relates to fact finding regarding possession of the invention.

Moreover, the Federal Circuit has recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact findings and its ultimate action. Dickinson v. Zurko, 119 S. Ct. 1816 (1999). In light of the Applicants arguments of record, and the presumption in favor of the Applicants, it is respectfully asserted that the Examiner's maintenance of the present rejection is not supported by substantial evidence, and as such, does not meet the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Examiner has not cited any relevant art nor relied on any other fact finding results which rebut the presumption in favor of the Applicants.

Thus, reconsideration and withdrawal of the rejection of the pending claims for failing to meet the requirements of 35 U.S.C § 112 pertaining to written description is respectfully requested. In the absence of withdrawal, Applicants respectfully request that the Examiner provided the factual basis, including reference to the art or personal knowledge which is being relied upon to maintain the rejection.

II. The subject matter of the pending claims is enabled

Claims 40-70 and 72-98 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection. Applicants assert that the claims recite subject matter which excludes naturally occurring species for such reasons as articulated above, e.g., because such embodiments have a benefit.

The test of enablement is whether one skilled in the art would be able to practice the claimed invention without undue experimentation. The scope of a claim should bear a reasonable relationship to the scope of subject matter enabled by the specification. MPEP 2164.01(b). Applicants are unaware of any legal basis for the Examiner's apparent conclusion that enablement under 35 USC §112 also requires experimentation to determine if an embodiment falls within the scope of a pending claim. Applicant assert that there is no foundation in 35 USC, 37 CFR, the MPEP or in the patent case law for a standard of enablement under 35 USC §112 which also requires that the practitioner of the claimed invention must be able to establish novelty of any particular embodiment covered by the claims.

Again, the examiner's attention is respectfully drawn to the analogy to the chemical arts discussed above.

Applicants submit that the present rejection is improper and should be withdrawn.

III. The claimed subject matter is patentable over the art

Claims 40-70, 72, 89-92, 94-95, and 97 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Park et al., in view of Mitchell et al., Harrison, and Schultz. Applicants respectfully traverse this rejection.

In maintaining the rejection of the pending claims over combinations of references that include Park et al., the Examiner argues that the teachings of that reference are very general with respect to techniques for creating composite DNA binding protein. However, the Examiner's arguments require that one skilled in the art engage in the impermissible task of selectively picking and choosing amongst (and selective ignoring) certain of the teachings of that reference using the present application as a template.

The Park et al. reference is not the broad generic teaching that the Examiner alleges. The Examiner states

> The fact remains is that the cited teachings are specifically generic: "We propose a general strategy for designing proteins... select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together... [Examiner's emphasis shown]

The manner in which fragments of the sentence have been presented to support the Examiner's position illustrate the danger which the courts have repeatedly articulated in admonishing the use of the patent disclosure as a template to pick and choose among isolated disclosures to demonstrate that the claims were obvious. Those portions of the sentence to which the Examiner refers as "..." are in fact the most instructive portion of that sentence with respect to how broad (or narrow) the teachings of the Park et al. reference actually are. That sentence, in its entirety, reads

> We propose a general strategy for designing proteins to recognize specific DNA-binding sites: this strategy is to select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together via a short peptide with cysteine crosslink in a way compatible with each peptide being able to bind to its own DNA segment. [emphasis added].

Considering the four corners of this reference, there is no support for the Examiner's argument for a broader scope to what it teaches. It is plain that, in its broadest sense, Park et al. is still limited to the use of cross-linking agents to generate chimeric DNA binding proteins from discontinuous polypeptide fragments. Park et al discloses the covalent "stitching" together of DNA-binding proteins to form a cysteine-crosslinked composite protein. That disclosure may be a general strategy for designing cysteine-crosslinked protein composites, but it does not in any way disclose the possibility of, or suggest the desirability of, designing, making or using nucleic acids.

Cysteine-crosslinked protein composites are different from nucleic acids encoding chimeric proteins and, indeed, from the encoded chimeric proteins themselves. That is presumably not controversial. The disclosure of one does not by itself suggest the other. The path from Park et al to the claimed invention was apparent to the examiner only because of the examiner's retrospective view provided by the teachings of the present application. Ironically, that path apparently never occurred to Park et al. That is evident from the omission by those authors of even a hint of the possibility or desirability of generating any recombinant nucleic acid constructs.

Moreover, the Examiner has failed to demonstrate how Park et al. bridges the gap between the claimed invention and the deficiencies which the Examiner admits for the remaining references of Mitchell et al., Harrison, and Schultz. Absent a suggestion of the asserted combination in any of the references themselves, the combination of these references is itself legally impressible with respect to maintaining a rejection for obviousness.

Withdrawal of the rejection of the pending claims under 35 USC 103 is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants hereby request that any fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: 21 March 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

40. (Twice Amended) A nucleic acid encoding a chimeric protein which binds a nucleic acid comprising a composite binding site, wherein the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site, wherein only one of the two nucleic acid-binding domains includes a zinc finger motif, and wherein the two nucleic acid-binding domains

(i) do not occur in the same protein in nature;

(ii) do not occur in the same protein in nature in the order in which they are present [inthe] in the chimeric protein; or

(iii) do not occur in nature with the same spacing that is present in the [chimericprotein] chimeric protein.

41. The nucleic acid of claim 40, wherein one nucleic acid-binding domain includes a zinc finger motif and the other nucleic acid-binding domain includes a motif or domain selected from the group consisting of a helix-loop-helix motif, a helix-turn-helix motif, and a basic domain.

42. The nucleic acid of claim 41, wherein the zinc finger motif is from a protein selected from the group consisting of transcription factor IIIA, SW15, Krüppel, Hunchback, and a steroid receptor.

43. The nucleic acid of claim 41, wherein the zinc finger motif is from Zif268.

44. The nucleic acid of claim 40, wherein one nucleic acid-binding domain includes a zinc finger motif and the other nucleic acid-binding domain includes a helix-turn-helix motif.

45. The nucleic acid of claim 44, wherein the other nucleic acid-binding domain includes a homeodomain.

46. The nucleic acid of claim 45, wherein the homeodomain is an Oct-1 homeodomain.

47. (Amended) The nucleic acid of claim 46, wherein the zinc finger motif is from a protein selected from the group consisting of transcription factor IIIA, Zif268, SW15, Krüppel, Hunchback, and a [streroid] steroid receptor.

48. The nucleic acid of claim 47, wherein the homeodomain is an Oct-1 homeodomain and the zinc finger motif is from Zif268.

49. The nucleic acid of claim 48, wherein the chimeric protein further comprises a second zinc finger of Zif268.

50. The nucleic acid of claim 49, which encodes ZFHD1.

51. The nucleic acid of claim 41, wherein the other nucleic acid-binding domain is from a protein selected from the group consisting of Daughterless, Achaete-scute (T3), MyoD, and E12 E47.

52. The nucleic acid of claim 41, wherein the other nucleic acid-binding domain is from a protein selected from the group consisting of MAT α1, MAT α2, MAT a1, Antennapedia, Ultrabithorax, Engrailed, Paired, Fushi tarazu, HOX, Unc86, Oct 1, Oct2, and Pit.

53. The nucleic acid of claim 41, wherein the other nucleic acid-binding domain is from a protein selected from the group consisting of GCN4, C/EBP, c-Fos, c-Jun, and JunB.

54. The nucleic acid of claim 41, wherein the zinc finger motif is from a steroid receptor.

55. The nucleic acid of claim 40, wherein the two nucleic acid-binding domains are separated by at least one amino acid.

56. The nucleic acid of claim 40, wherein the chimeric protein binds with higher affinity to the composite binding site than to each of the portions of the composite binding site to which each of the two nucleic acid binding domains bind.

57. The nucleic acid of claim 40, wherein the chimeric protein further comprises an additional domain.

58. The nucleic acid of claim 57, wherein the additional domain is a regulatory domain.

59. The nucleic acid of claim 58, wherein the regulatory domain is an activation domain.

60. The nucleic acid of claim 59, wherein the activation domains is an Herpes Simplex Virus VP16 activation domain.

61. The nucleic acid of claim 58, wherein the regulatory domain is a repression domain.

62. The nucleic acid of claim 61, wherein the repression domains is from a Krüppel protein.

63. The nucleic acid of claim 57, wherein the additional domain is a nucleic acid cleavage domain.

64. The nucleic acid of claim 63, wherein the nucleic acid cleavage domain is the FokI cleavage domain.

65. The nucleic acid of claim 57, wherein the additional domain is selected from the group consisting of a domain interacting with a cellular component, a domain which controls the stability of the chimeric protein, and a domain which controls subcellular localization.

66. A nucleic acid encoding a chimeric protein which binds a nucleic acid comprising a composite binding site, wherein the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site, wherein only one of the two nucleic acid-binding domains includes a DNA binding domain from a protein comprising a homeodomain, and which nucleic-acid binding domains

(i) do not occur in the same protein in nature;

(ii) do not occur in the same protein in nature in the order in which they are present in the chimeric protein; and/or

(iii) do not occur in nature with the same spacing that is present in the chimeric protein.

67. The nucleic acid of claim 66, wherein one nucleic acid-binding domain includes a helix-turn-helix motif and the other nucleic acid-binding domain includes a motif or domain selected from the group consisting of a zinc finger motif, a helix-loop-helix motif, and a basic domain.

68. The nucleic acid of claim 66, wherein the chimeric protein further comprises an activation domain.

69. The nucleic acid of claim 66, wherein the chimeric protein further comprises a repression domain.

70. The nucleic acid of claim 66, wherein the chimeric protein further comprises an nucleic acid cleavage domain.

72. A vector comprising a nucleic acid of claim 40.

73. The vector of claim 72, further comprising expression control sequences permitting gene expression in eukaryotic cells.

74. A kit comprising a nucleic acid of claim 72 and a gene operably linked to a composite binding site to which the chimeric protein encoded by the vector binds.

75. A method for modulating expression of a gene in a cell, comprising expressing a chimeric protein in a cell which includes a gene operably linked to a composite binding site to which the chimeric protein binds, wherein the chimeric protein comprises two nucleic acid-binding domains, each of which binds a sequence which is a portion of the composite binding site, and which nucleic acid-binding domains

(i) do not occur in the same protein in nature;

(ii) do not occur in the same protein in nature in the order in which they are present in the chimeric protein; and/or

(iii) do not occur in nature with the same spacing that is present in the chimeric protein,

whereby the chimeric protein binds the composite binding site, thereby modulating expression of the gene in the cell.

76. The method of claim 75, wherein the chimeric protein further comprises an additional domain.

77. The method of claim 76, wherein the additional domain is a regulatory domain.

78. The method of claim 77, wherein the regulatory domain is an activation domain.

79. The method of claim 78, wherein the activation domain is an Herpes Simplex Virus VP16 activation domain.

80. The method of claim 77, wherein the regulatory domain is a repression domain.

81. The method of claim 75, wherein one nucleic acid-binding domain includes a zinc finger motif and the other nucleic acid-binding domain includes a motif or domain selected from the group consisting of a basic domain, a helix-loop-helix motif, and a helix-turn-helix motif.

82. The method of claim 81, wherein the other domain is a homeodomain.

83. The method of claim 75, wherein the chimeric protein further comprises an additional nucleic acid-binding domain, which binds a sequence which is a portion of the composite binding site.

84. The method of claim 83, wherein the additional nucleic acid-binding domain includes a zinc finger motif.

85. A method for producing a cell for use in the method of claim 75, comprising introducing into a cell a nucleic acid encoding the chimeric protein.

86. A method for producing a cell for use in the method of claim 75, comprising introducing into a cell a nucleic acid comprising a composite binding site.

87. The method for claim 86, further comprising introducing into the cell a nucleic acid encoding the chimeric protein.

88. The method of claim 87, wherein the gene encodes a recombinant gene product.

89. The nucleic acid of claim 66, wherein one nucleic acid-binding domain includes a homeodomain.

90. The nucleic acid of claim 40, further comprising an additional nucleic acid-binding domain, which binds a sequence which is a portion of the composite binding site.

91. The nucleic acid of claim 66, further comprising an additional nucleic acid-binding domain, which binds a sequence which is a portion of the composite binding site.

92. The nucleic acid of claim 71 further comprising an additional nucleic acid-binding domain, which binds a sequence which is a portion of the composite binding site.

93. The nucleic acid of claim 75, further comprising an additional nucleic acid-binding domain, which binds a sequence which is a portion of the composite binding site.

94. The nucleic acid of claim 57, wherein the additional domain is heterologous with respect to the two nucleic acid-binding domain.

95. The nucleic acid of claim 68, wherein the activation domain is heterologous with respect to the two nucleic acid-binding domains.

96. The method of claim 76, wherein the additional domain is heterologous with respect to the two nucleic acid-binding domains.

97. The nucleic acid of claim 40, which encodes a chimeric protein which binds the composite binding site that is not a naturally-occurring binding site of a naturally-occurring transcription factor.

98. The nucleic acid of claim 66, which encodes a chimeric protein which binds the composite binding site that is not a naturally-occurring binding site of a naturally-occurring transcription factor.